REMARKS

I. Pending Claims

The Office Action mailed December 15, 2003 rejecting claims 77-81, 84, 86, 87, 89 and 91-106 has been received and its contents carefully noted. Claims 1-76 have been withdrawn. Claims 82, 83, 85, 86, 88, and 90 have been cancelled. New claims 107-112 have been added.

The applicant has previously elected Group II, with traverse (encompassing claims 77 to 109 directed to a pharmaceutical composition). The applicant also wishes to include additional claims directed toward methods of using the composition according to the invention which are presented as new claims 110 to 112 in the attached set of amended claims. Claims 107-109 track claims 78, 95 and 101, respectively, without nifedipine. Claims 110-112 are method claims depending from the three independent composition claims, and satisfy the standards for joinder.

The amendments cancel claims, comply with formal requirements, and put the claims in condition for allowance or appeal, and applicant asks that they be entered into the case. Upon entry of this amendment, thirty claims are pending: three independent claims 77, 94 and 100; and 27 dependent claims 78-81, 84, 87, 89, 91-99 and 101 -112.

II. Response to Examiners Rejections

A. Claim Rejections - 35 U.S.C. §102

The Examiner maintains that Currently Amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 105 are anticipated by Antropoli (WO 98/37886).

Antropoli fails to anticipate the claimed invention because the cited reference is not enabling for a composition comprising:

a pharmaceutically acceptable carrier;

a compound chosen from a potassium channel opener, a potassium channel agonist and an adenosine receptor agonist; and

a local anaesthetic;

wherein the compound and local anaesthetic are present in the composition in amounts sufficient to either arrest the heart, protect an organ, or preserve an organ; and

wherein the pharmaceutically acceptable carrier includes potassium at a concentration of less than about 10mM.

Antropoli concerns topical soothing anal preparations of nifedipine, a known *calcium* antagonist. At page 4, lines 17 to 21, nifedipine is stated to have been "proven to play a crucial role in inhibiting the flow of Ca++ ions into the sarcoplasm of the smooth muscle cells which is known to cause a contraction of muscle fibres." The medicament is administered externally to the affected area with the effect to induce relaxation of vascular walls of the anal canal. The examples refer to the application of a gel containing a local anaesthetic in control patients *or* a gel containing nifedipine in the test patients. There is no suggestion that these two components would be administered together or simultaneously in a single preparation or composition.

Antropoli does not enablingly disclose a composition comprising both the compound and local anesthetic in a single preparation in the amounts as required by the claims. Antropoli relates only to topical application of nifedipine, and does not teach or direct the person skilled in the art to a composition that can be administered by any other means, for example parenteral administration (see for example, page 9, lines 1 to 5 and Examples). Antropoli does not anticipate the claims. In particular, new claims 107-109 do not include nifedipine, and the other claims require sufficient amounts of the compound and anesthetic, not disclosed in Antropoli.

The Examiner maintains that Amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 105 are anticipated by Homeister et al (1990). Homeister fails to anticipate the claimed invention.

Homeister administers an intravenous bolus of lidocaine in open chested

dogs 1 minute before a 90 minute occlusion of the left circumflex coronary artery and again 1 minute before reperfusion. Only at reperfusion, after ischaemia, does Homeister suggest adenosine be infused (through an intercoronary catheter) and continued for one hour. Adenosine and lidocaine were not administered simultaneously in a single preparation or composition. Moreover, a composition comprising both a compound and a local anaesthetic in a single preparation is not disclosed.

Where Homeister discusses "adenosine plus lidocaine", or "combined treatment", the reference does not in fact teach nor suggest a composition as claimed in this application. As set out in the previous paragraph, Homeister specifically teaches pre-treatment with lidocaine (as a bolus injection), no treatment during ischaemia, and a second bolus injection of lidocaine followed by continuous adenosine administration at reperfusion (Homeister, page 597, left column). No composition as now claimed is taught. Thus, "combined" is used to mean used in the one experiment sequentially, not to mean "together" as required by the claims of this application.

Moreover, even with the sequential administration taught, Homeister's results were not repeatable to the extent they showed any success. This significantly limits the significance a skilled person would put on Homeister as far as what it teaches. Although his experiments allegedly showed reduced infarct size by administering adenosine to animals (dogs) *pretreated* with lidocaine, these results have not been repeatable, as later reported by Vander Heide & Reimer (see *Cardiovascular Research*, 33: 499-500 (1997)). In fact, Vander Heide & Reimer found no beneficial effect of lidocaine with adenosine. Thus, Vander Heide & Reimer shows that Homeister does not enablingly disclose a combination of the compound and local anaesthetic of the subject invention in a single preparation. In fact, Vander Heide comments that Homeister did not include the animals that died in his results, thus casting further doubt on the conclusions suggested by Homeister. Consistently with this doubt, Mahaffey (see below) reached the opposite conclusion to Homeister.

The Examiner maintains that amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 105 are anticipated by Garratt et al.

In Garratt, lidocaine and adenosine were administered sequentially and separately in humans during balloon angioplasty and thrombolytic therapy respectively. Thus, adenosine and lidocaine were not combined into a single preparation or composition, nor is such preparation taught by Garratt et al. A number of other drugs were also administered at the same time, in the discretion of the physician (p. 197, left column). Furthermore, there was no suggestion that the administration of lidocaine when administered sequentially and separately from adenosine or other drugs provided any additional benefit.

This is later supported by Mahaffey et al (see *JACC*, 34(6):1711-1720(1999)), where it was concluded that no additional benefit is gained from the administration of lidocaine separately to the administration of adenosine. Homeister's work in 1990 was followed by Garratt in 1998 and Mahaffey in 1999. Where lidocaine and adenosine were both administered, they were administered separately. In 1999, citing prior studies including Homeister and Garratt, Mahaffey concluded that there was no benefit in administering lidocaine to patients in conjunction with adenosine:

> *"...there was no difference in the treatment effect of adenosine by lidocaine use. These data suggest that lidocaine need not be given in conjunction with adenosine."*

(Mahaffey, p.1717, 2nd column)

Thus, the latest study in 1999 taught no benefit in administering adenosine following lidocaine, let alone administering them together in a single composition.

Accordingly, like Homeister, Garratt et al. does not anticipate the claimed invention.

The Examiner maintains that amended claims 77, 78, 80 to 81, and new

claims 94, 95, 97, 98, 100, 101, and 103 to 105 are anticipated by Jayawant et al. (1998).

This document reviews whether myocardial protection can be obtained with pinacidil (potassium channel opener) and its effect compared to the traditional high potassium arrest solution, St. Thomas' Hospital solution. The hearts used in this study were divided into three different groups receiving various cardioplegic regimens:

GROUP 1 : control solution consisting of Krebs-Henseleit solution alone;

GROUP 2: hyperkalemic (high potassium) cardioplegia with St. Thomas' Hospital solution; and

GROUP 3: hyperpolarising cardioplegia with pinacidil in Krebs-Henseleit solution, the initial pinacidil infusion containing procaine (page 133, end of column 1).

All three groups were divided into a further two groups where the solutions were delivered either (a) intermittently, or (b) continuously.

GROUP 1 were treated with neither a compound as defined in the present claims (i.e., potassium channel opener or adenosine agonist) nor a local anesthetic. GROUP 2 were treated with a hyperkalemic composition, meaning the potassium concentration is well over 10 mM. The GROUP 3(a) hearts were treated with "intermittent boluses of 50μmol/L pinacidil and was administered with procaine in small doses (5mmol/L at 0 minutes, 2mmol/L at 20 minutes and 40 minutes..." (page 133, top of column 2). No procaine was delivered with pinacidil when it was delivered continuously, perhaps because the authors found that there was no significant difference in the results between the intermittent pinacidil groups with and without the procaine boluses, ie, the local anesthetic procaine had *no effect*.

Accordingly, Jayawant does not teach a combination composition according

to the invention comprising:

a pharmaceutically acceptable carrier;

a compound chosen from a potassium channel opener, a potassium channel agonist and an adenosine receptor agonist; and

a local anaesthetic;

wherein the compound and local anaesthetic are present in the composition sufficient to either arrest the heart, protect an organ, or preserve an organ; and

wherein the pharmaceutically acceptable carrier includes potassium at a concentration of less than about 10mM.

B. Claim Rejections - 35 U.S.C. §103

The Examiner considers that Amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 106 are unpatentable in light of Jayawant.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. As mentioned above, Jayawant explores whether myocardial protection can be obtained with pinacidil (a potassium channel opener) and its effect compared to the traditional high potassium concentration arrest solution, St. Thomas' Hospital solution. Jayawant discloses a composition containing pinacidil in Krebs-Henseleit buffer where procaine (a local anesthetic) is only used with pinacidil in the intermittent doses of that solution. *The local anesthetic was found not to affect pinacidil's protective effect during prolonged arrest.* As stated by the authors, the addition of the procaine in all pinacidil infusions may have eliminated all electrical activity but did not improve functional recovery. Accordingly, Jayawant does not teach or suggest an effective composition including pinacidil and procaine in a single composition for arrest

protection or preservation of an organ, and in particular for arrest, protection or preservation of the heart. In fact, Jayawant concludes that the pinacidil should be given continuously, but not procaine. Thus it does not teach both in the same composition, and teaches away from that approach, as claimed here.

The deficiencies in Jayawant are not taught by Raymond. Raymond discloses an organ transplant solution, with a Krebs-Henseleit bi-carbonate solution having up to 30mM potassium. Raymond states in the passage following table 1, when used as a cardioplegia, 20-30mM potassium is required. One of the advantages of the present invention over the prior art is to avoid the side-effects of such high potassium found in prior cardioplegic compositions.

Moreover, Raymond does not teach the addition of a local anesthetic to the solution. A skilled person in the art is not motivated to combine Raymond and Jayawant to obtain the composition according to the subject invention, particularly in light of Jayawant's conclusion that the local anaesthetic did not provide a benefit in cardioplegia. Jayawant does not render obvious the claims to cardioplegic compositions with low potassium, and does not teach or suggest the organ protection and organ preserving solutions of the other claims.

This can be further supported by reviewing the specific concentrations of potassium used in Raymond's solutions. Referring to Table 1, the concentration of KCl is listed provided at 3.0mM to 30mM, i.e., from non-arresting to arresting concentrations of potassium. The non-arresting solutions are not pertinent to Jayawant's teachings. Referring to Raymond's specific examples of 'cardioplegic solution' (see column 6, example 1) KCl is provided at an arresting concentration of 30mM. Thus Raymond teaches a hyperkalemic arrest solution and thus would not be motivated to combine the teaching of Raymond with Jayawant to obtain a composition according to the present invention with potassium below about 10mM.

The inventor maintains that the subject invention is patentable in light of Jayawant in view of Raymond.

The Examiner considers that Amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 105 are unpatentable over Garratt et al in view of Glasser et al.

As explained above, Garratt et al. discloses the separate administration of lidocaine and adenosine, i.e. not in a single composition. Thus, Garratt et al. does not disclose, teach or suggest a composition according to the subject invention

The deficiencies of Garratt et al. are not remedied by the teachings of Glasser et al. Glasser et al. is directed to the production and use of soluble analogues of thrombomodulane that retain activity after exposure to oxidants. These analogues are manufactured using recombinant DNA technology and are useful in, for example, antithrombotic therapies. Thrombomodulane is known to have anticoagulant properties and useful for anticoagulant therapy. Glasser et al states that there is a need for soluble thrombomodulane which is resistant to inactivation by exposure to oxidants and easily produced in large quantities. The Examiner directs the applicant to the passage in Glasser et al at column 9 lines 5 to 12 where it is stated that streptokinase is commonly used to treat acute myocardial infarction. This document does not direct the person skilled in the art to administer a compound (as defined in the claims of this application) and a local anaesthetic in a single composition. Nor does this document motivate a person skilled in the art to administer streptokinase with the composition according to the invention, or suggest any advantage in doing so, because the literature did not demonstrate any efficacy.

Garratt and Jayawant (using different approaches from the subject application) found no effect, and Homeister's alleged limited success was later contradicted.

Finally, it is not legitimate to select prior art documents with the benefit of hindsight. A skilled person at the priority date would also have looked at recent clinical reports, such as Mahaffey referred to above in section 5. As the excerpt quoted there states, in 1999, the evidence did not support a combination of adenosine and lidocaine and thus taught away from the invention of this application.

Thus, the skilled person would not be motivated to combine the two documents and accordingly the composition of the present application is patentable over Garratt et al in view of Glasser et al.

The Examiner considers that Amended claims 77, 78, 80 to 81, and new claims 94, 95, 97, 98, 100, 101, and 103 to 105 are unpatentable over Garratt or Homeister.

Although both Garratt and Homeister describe an example of the separate administration of adenosine and lidocaine, neither document teaches a composition where adenosine and lidocaine are administered simultaneously in a single composition. As stated above, Homeister does not teach or suggest a composition including adenosine and lidocaine in a single preparation. Further Vander Heide & Reimer were not able to reproduce Homeister's results, with the administration of adenosine to lidocaine treated animals. This further teaches away from the composition according to the subject invention.

Garratt concluded that there was no benefit of the addition of lidocaine to adenosine. This is later supported by Mahaffey et al (see *JACC*, 34(6):1711-1720(1999)), where it was concluded that no additional benefit is gained from the administration of lidocaine separately to the administration of adenosine.

Accordingly, both documents teach away from a composition as claimed comprising:

a pharmaceutically acceptable carrier;

a compound chosen from a potassium channel opener, a potassium channel agonist and an adenosine receptor agonist; and

a local anaesthetic;

wherein the compound and local anaesthetic are present in the composition sufficient to either arrest the heart, protect an organ, or preserve an organ; and

wherein the pharmaceutically acceptable carrier includes potassium at a concentration of less than about 10mM.

Both Garratt and Homeister teach that there was no additional benefit to be gained from the addition of lidocaine to adenosine. A person skilled in the art would not have been motivated to combine a compound and a local anaesthetic into an effective single composition, particularly in light of the findings disclosed in Vander Heide and Mahaffey.

In contrast, the subject invention demonstrates that a composition comprising a compound (as defined) and local anaesthetic in a single preparation results in an improved result for arresting, protecting or preserving an organ, especially the heart. The prior art at the date of the subject application teaches away from such a composition. In fact, the lack of published work in this field (other than the applicant's own patent applications) after Mahaffey is indicative that experts had abandoned this line of enquiry as not being successful.

IV. Conclusion

In view of the foregoing, it is believed that none of the pending claims 77-81, 83, 84, 87, 89 and 91-112 are anticipated or obvious over the cited references. All claims are now believed to be in condition for allowance.

Respectfully submitted,

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